REMARKS

After entry of this paper, claims 59-61 are pending. Claims 1-58 are cancelled in an effort to place the application in condition for allowance and to clarify the invention. Applicants reserve the right to pursue the non-elected subject matter and claims in a divisional application. No new matter has been added.

Claims and Claim Support

New claims 59-61 are drawn to "kits" and properly contain elected subject matter. Specifically, new claim 59 specifies a kit which contains a gastrin/CCK receptor ligand and an EGF receptor ligand in specific amounts. These amounts are supported by, and were calculated based on, the dosages provided in the specification at page 12, lines 29-32 and at page 15, line 26 through page 16, line 8 and knowledge in the art. As the Examiner is aware, it is widely accepted in the art, and has been from prior to the priority date of this invention, that unit dosages are routinely calculated based on an about 70 kg human subject. To support this assertion, Applicants enclose a copy of a document from the Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, which is also included in the Supplemental IDS submitted on this date. This document discusses the use of body weight in calculating dose (mg/kg body weight), and includes reports by five (5) task groups on studies performed from 1975 to 1997 regarding the standard weight for a reference human subject. As the Examiner will note, all of the reports are consistent in that the weight for a reference human subject is about 70 kg. Thus, the therapeutically effective amount recited in the claims is supported by the original specification and does not present new subject matter.

New claim 60 provides examples of EGF receptor ligands and is supported at page 8, lines 6-12 of the specification.

New claim 61 provides examples of gastrin/CCK receptor ligands and is supported at page 7, lines 26-27 of the specification.

Applicants also maintain that the pending claims are fully supported by the earliest priority document, i.e., US Patent Application No. 07/992,255, now US Patent No. 5,885,956.

(*See, e.g.*, the support for the pending claims at col. 3, lines 60-62; col. 4, lines 14-25; col. 6, lines 23-64; and col. 7, lines 1-8 in US Patent No. 5,885,956).

No new matter is added by these new claims.

35 USC § 102(b) Rejection

Claims 44-56 are rejected under this section for assertedly being anticipated by Conteas et al. (Proc. Soc. Exp. Biol. Med 184(3): 307-311, 1987). The Examiner asserted that "...it would be fair to conclude that the gastrin and EGF were in vials for shipment and were in closed proximity to one another at some point in time..." and that "[t]his would constitute a "kit"...".

Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The cancellation of claims 44-56 renders the outstanding rejection moot as applied to these claims. However, Applicants present the following comments regarding the novelty of new claims 59-61 over <u>Conteas</u>. <u>Conteas</u> discusses the exposure of a small intestinal crypt cell line to gastrin and EGF *in vitro* and the determination of DNA synthesis by the cells in culture. <u>Conteas</u> does not disclose the presently claimed kits, and particularly the therapeutically effective amount of a gastrin/CCK receptor ligand or EGF receptor ligand recited in the claims, i.e., about 1.4 to about 35 mg. Therefore, <u>Conteas</u> does not teach the pending claims. Reconsideration of this rejection is requested.
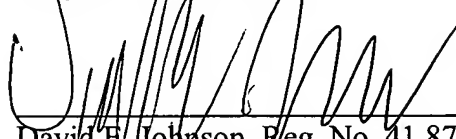
Double Patenting Rejection

Claim 52 is rejected on the group of nonstatutory obviousness-type double patenting as assertedly unpatentable over claim 7 of US Patent No. 6,288,301 ('301). The Examiner asserted that "...a "kit" does not distinguish the pharmaceutical composition of the instant claim from the pharmaceutical composition of the patented claim".

The filing of the enclosed Terminal Disclaimer renders the outstanding rejection moot.

Applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

Dated: October 30, 2007

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Air Toxics Hot Spots Program
Risk Assessment Guidelines

Part IV
Technical Support
Document for
Exposure Assessment
and Stochastic
Analysis

September 2000

Secretary for Environmental Protection
California Environmental Protection Agency
Winston H. Hickox

Director
Office of Environmental Health Hazard Assessment
Joan E. Denton, Ph.D.

Final Draft

September 2000

**Air Toxics Hot Spots Program
Risk Assessment Guidelines
Part IV**

Technical Support Document

Exposure Assessment and Stochastic Analysis

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay Street, 16th Floor
Oakland, California 94612 (510) 622-3200

Technical Support Document for Exposure Assessment and Stochastic Analysis
September 2000

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10.   Body Weight

10.1   Introduction

Body weight is an important variate in risk assessment that is used in calculating dose (mg/kg*body wt). Many of the studies that OEHHA used to generate the distributions and point estimates collected body weight data on the subjects in the study. The consumption rate for each subject was divided by the body weight of that subject, and distributions of consumption per unit body weight per day were generated. However a few of the studies, such as the one used to determine fish consumption rate, did not collect body weight information on the subjects. Therefore a review of the body weight literature was conducted and appropriate body weight defaults were selected for our purposes. The published literature on body weight is mainly based on data gathered in the first National Health and Nutrition Examination Survey conducted between 1970 and 1974, and more recently in the second National Health and Nutrition Examination Survey (NHANES II).

10.2   Empirical Distributions

10.2.1   NHANES II (U.S.EPA, 1997)

NHANES II was conducted on a nationwide sample of about 28,000 persons, aged 6 months to 74 years, from the civilian, non-institutionalized population of the United States. The sample was selected so that certain 'at risk' subgroups (low income, preschool children, elderly) were over sampled. Since the survey was meant to be representative of the U.S. population, the raw data were weighted to reflect the age structure, sex and race of the population at the time of the survey. The survey began in 1976 and was completed in 1980. The mean body weights of adults and children and their standard errors are given in Table 10.1. The average value of 71.8 kg for adults is the basis for the human default value of 70 kg.

10.2.2   Report of the Task Group on Reference Man (ICRP, 1975)

This task group of the International Commission on Radiological Protection (ICRP) reviewed and compiled extensive data on anatomical measurements, elemental composition, and physiological values for the human body. Weight (W), length (L), and surface area (SA) during prenatal life are presented as means +/- standard deviation (SD) as a function of gestational age. The data are based on 13,327 cases. From the data, a number of allometric relations were derived which relate gestational age to average length, and length to surface area and weight. Postnatal life data from a number of sources were reviewed. In addition to charts showing mean body weight ± one SD from 0 to 12 years and from 0 to 56 years by sex, the following defaults were recommended:

Newborn male: mean = 3.5 kg; SD = ± 0.59 kg;
Newborn female: mean = 3.4 kg; SD = ± 0.59 kg;
Adult male: mean = 71.7 kg; SD = ± 10 kg;
Adult female: mean = 56.7 kg; SD = ± 8.6 kg.

Tabular data relating height in cm to body weight in kg for 8 age groups 18-79 years are given for the 25th, 50th and 75th percentiles. These data are summarized in Table 10.2 for the reference total body heights of 170 cm for males and 160 cm for females.

10.2.3   NCHS (Hamill et al. 1979)

The National Center for Health Statistics (NCHS) prepared percentile curves for assessing the physical growth of children ages 0 to 36 months. Smoothed percentile curves were derived for body weight, length, and head circumference. Separate sets were produced for male and female children. The data used were from the Fels Research Institute, Yellow Springs, Ohio. Body weight percentiles of 5th, 10th, 25th, 50th, 75th, 90th, and 95th are given for ages of 0 (birth), 1, 3, 6, 9, 12, 18, 24, 30, and 36 months for each sex. The data were smoothed by cubic spline approximation.

10.3   Modeled Distributions

10.3.1   Brainard and Burmaster, 1992

These authors examined data on height and weight of adults from NHANES II and fit bivariate distributions to the tabulated values for men and women separately. The survey tabulated the height and weight of 5916 men and 6588 women aged 18-74. After statistically adjusting the raw data to reflect the whole U.S. population aged 18-74 for age structure, sex, and race the U.S. Public Health Service published results for an estimated 67,552 men and 74,167 women. Defining the variables height (Ht) in inches and weight (Wt) in pounds the authors observed that the marginal histograms for Ht were symmetrical and for Wt were positively skewed. Consequently they defined and analyzed the additional variable lnWt for each sex. For men straight lines were fit to cumulative values and z-scores for lnWt and Ht with R^2 values of 0.999. For weight (lb), the estimated values of $\mu \pm \sigma$ for men are exp (5.13 ± 0.17). For women the visual fit of the line to lnWt was not as good, but adequate. The estimated values (lb) of $\mu \pm \sigma$ are exp(4.96 ± 0.20). The body weight arithmetic mean (lb) and standard deviation for men and women are 171 ± 29.4 and 145 ± 29.4. The body weight mean and standard deviation in kg for men and women are 77.9 ± 13.3 and 66.1 ± 13.6, respectively. The conversion from $\mu \pm \sigma$ to arithmetic mean and standard deviation is done using the following formulas (Burmaster and Hull, 1997).

$$Amean = exp(\mu + 0.5 * \sigma^2)$$

$$AStdDev = exp(\mu) * \sqrt{exp(\sigma^2) * [exp(\sigma^2) - 1]}$$

10.3.2   Finley et al., 1994

These authors summarize body weight distributions analyzed by Brainard and Burmaster and present a combined standard distribution for equal numbers of adult men and women of 71.0 ± 15.9 kg. The 50th and 95th percentiles of the combined distribution are 70 and 101 kg,

respectively. The distributions for adult males and females are given as 78.7 ± 13.5 kg and 65.4 ± 15.3 kg, respectively. Finley et al. also present annual age group weight distributions for children 18 years of age and under (Table 10.3). These distributions are considered by the authors to reflect almost entirely interpersonal variation due to the large sample sizes and consistent methodology used in the NHANES II survey.

10.3.3 Burmaster et al. 1977

In this paper, Burmaster et al. 1997 fit normal and lognormal distributions to the male and female child data sets from the NHANES II Survey. The authors concluded that the lognormal distributions consistently fit the points better than did normal distributions.

Table 10.1 Body Weight of Adults and Children from NHANES II (kg)[a]

Age Group, yr	Male		Female		Male & Female
	Mean	Std Dev	Mean	Std Dev	Mean
Adults (Years)					
18<25	73.8	12.7	60.6	11.9	67.2
25<35	78.7	13.7	64.2	15.0	71.5
35<45	80.9	13.4	67.1	15.2	74.0
45<55	80.9	13.6	68.0	15.3	74.5
55<65	78.8	12.8	67.9	14.7	73.4
65<75	74.8	12.8	66.6	13.8	70.7
18<75	78.1	13.5	65.4	14.6	71.8
Children					
6-11 months	9.4	1.3	8.8	1.2	9.1
1 year	11.8	1.9	10.8	1.4	11.3
2 year	13.6	1.7	13.0	1.5	13.3
3 year	15.7	2.0	14.9	2.1	15.3
4 year	17.8	2.5	17.0	2.4	17.4
5 year	19.8	3.0	19.6	3.3	19.7
6 year	23.0	4.0	22.1	4.0	22.6
7 year	25.1	3.9	24.7	5.0	24.9
8 year	28.2	6.2	27.9	5.7	28.1
9 year	31.1	6.3	31.9	8.4	31.5
10 year	36.4	7.7	36.1	8.0	36.3
11 year	40.3	10.1	41.8	10.9	41.1
12 year	44.2	10.1	46.4	10.1	45.3
13 year	49.9	12.3	50.9	11.8	50.4
14 year	57.1	11.0	54.8	11.1	56.0
15 year	61.0	11.0	55.1	9.8	58.1
16 year	67.1	12.4	58.1	10.1	62.6
17 year	66.7	11.5	59.6	11.4	63.2
18 year	71.1	12.7	59.0	11.1	65.1
19 year	71.7	11.6	60.2	11.0	66.0

[a] From U.S. EPA, 1997

Table 10.2   Median and Quartile Human Body Weights by Age; United States, 1960-2[a]

Age Group, yr	25%	50%	75%
Males			
18-24	63	68	76
25-34	67	74	85
35-44	68	74	81
45-54	68	75	85
55-64	67	76	85
65-74	64	72	78
75-79	66	83	88
18-79	66	73	82
Females			
18-24	51	55	60
25-34	52	58	66
35-44	57	63	73
45-54	57	64	73
55-64	61	68	82
65-74	60	65	74
75-79	55	66	71
18-79	56	62	72

[a] Weights in kg for reference heights of 170 cm male, 160 cm female
(Adapted from ICRP, 1975)

Table 10.3   **Summary of Distribution Factors for Body Weight by Age**[a]

Age, yr	Arithmetic Mean, kg	SD, kg
0.5-1	9.4	1.2
1-2	11.8	1.4
2-3	13.6	1.6
3-4	15.7	1.7
4-5	17.8	2.3
5-6	20.1	2.8
6-7	23.1	3.5
7-8	25.1	3.8
8-9	28.4	5.2
9-10	31.3	5.0
10-11	37.0	7.5
11-12	41.3	10.5
12-13	44.9	10.0
13-14	49.5	10.5
14-15	56.6	10.3
15-16	60.5	9.7
16-17	67.7	11.6
17-18	67.0	11.5

[a] Adapted from Finley et al. (1994).

10.4 Recommendations

10.4.1 Point Estimate Approach

The point estimates for body weight in kg for 9, 30 and 70 years are calculated by taking the time weighted average of the mean body weights for ages 0.5 through 9, and ages 0.5 through 70 as presented in Table 10.1. In the interest of simplicity males and females are averaged. If a toxicant affects only one or predominantly one gender, the assessor may want to adjust point estimates and distributions of intake parameters to reflect body weight of the gender in question; however, such an adjustment will not result in a significant change in the results of the risk assessment. For the 30-year exposure scenario, the body weight for the 70-year scenario can be used in the interest of simplicity. The use of the time-weighted average approach allows for a more accurate calculation of dose from ages 0-9 and ages 0-70 because an estimate of the change in body weight as an individual grows is factored in.

Table 10.4 Point Estimates for Body Weight (kg)

	Ages 0-9	Age 0-70
Body weight	18	63

10.4.2 Distributions for Stochastic Approach

OEHHA is not recommending distributions for a stochastic approach because most of the consumption rate distributions that we derive from raw data, or recommend from the literature already incorporate subject body weight. It may be appropriate to use body weight distributions when the correlation between body weight and the consumption rate of interest is known. For the fish consumption distribution we have chosen to divide the consumption distribution by a point estimate of body weight because the correlation is not known. If body weight distributions are used without the appropriate correlation broad distributions are generated that may overestimate the variability in the parameter of interest. The available data in the literature may be adequate to generate approximate ages 0-9 and ages 0-70 body weight distributions if such distributions are needed.

10.5   References

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